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Invited paper

ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer☆

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Summary

The European Society of Thoracic Surgeons (ESTS) organized a workshop dealing with lymph node staging in non-small cell lung cancer. The objective of this workshop was to develop guidelines for definitions and the surgical procedures of intraoperative lymph node staging, and the pathologic evaluation of resected lymph nodes in patients with non-small cell lung cancer (NSCLC). Relevant peer-reviewed publications on the subjects, the experience of the participants, and the opinion of the ESTS members contributing on line, were used to reach a consensus. Systematic nodal dissection is recommended in all cases to ensure complete resection. Lobe-specific systematic nodal dissection is acceptable for peripheral squamous T1 tumors, if hilar and interlobar nodes are negative on frozen section studies; it implies removal of, at least, three hilar and interlobar nodes and three mediastinal nodes from three stations in which the subcarinal is always included. Selected lymph node biopsies and sampling are justified to prove nodal involvement when resection is not possible. Pathologic evaluation includes all lymph nodes resected separately and those remaining in the lung specimen. Sections are done at the site of gross abnormalities. If macroscopic inspection does not detect any abnormal site, 2-mm slices of the nodes in the longitudinal plane are recommended. Routine search for micrometastases or isolated tumor cells in hematoxylin-eosin negative nodes would be desirable. Randomized controlled trials to evaluate adjuvant therapies for patients with these conditions are recommended. The adherence to these guidelines will standardize the intraoperative lymph node staging and pathologic evaluation, and improve pathologic staging, which will help decide on the best adjuvant therapy.

Keywords: Lung cancer; Intraoperative lymph node staging; Pathologic evaluation of lymph nodes

1. Introduction

Defining the stage of a malignant disease is key for planning therapy, estimating prognosis and for comparison of studies [1]. The extent of lymph node involvement in patients with non-small cell lung cancer (NSCLC) is the most important prognostic factor and influences therapeutic strategies [2]. There are internationally accepted definitions for lymph node staging in NSCLC, however, there are some unanswered questions regarding extent, nomenclature definition, and surgical procedure of intraoperative lymph node evaluation. Furthermore, the quality of pathologic assessment is ill-defined and may vary between observers [3].

The council of the European Society of Thoracic Surgeons (ESTS) initiated a workshop which took place in Zurich on 25th March and 6th July 2004 in order to standardize definitions, surgical procedures, and pathologic evaluation.

☆ The first ESTS Workshop was organized during the first ESTS Spring Meeting March 2004 Zurich Switzerland and was presented at the second ESTS Spring Meeting April 2005 Athens Greece.

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Based on peer-reviewed publications with a level of evidence from II to IV [4], these guidelines were open for discussion on the society's website for its members and the relevant replies were integrated in the final document.

A second manuscript dealing with the preoperative evaluation of intrathoracic lymph node status in patients with NSCLC will be published in the near future as the result of a second ESTS workshop.

2. Anatomy and lymph drainage of the lungs

Three planes of lymphatic drainage from the lungs are of clinical importance: anterior, mediastinal, and posterior (intercostal) routes. Several studies have demonstrated a great anatomical variability of the lymphatic system of the lungs which might serve as possible explanation for the somewhat unpredictable pattern of lymphatic metastases of lung tumors [5].

From the surgical point of view it is important to note that segmental and subpleural lymphatics may drain directly to paratracheal or supraclavicular stations which is a possible explanation for skip metastases to these lymph node stations without involvement of intrapulmonary or hilar nodes [6]. In a study of 179 patients undergoing bronchial lymphoscintingraphy during investigation for NSCLC [7], mediastinal skip metastases identified in 25% of cases. In addition, crossover lymphatic drainage across the midline was frequently found. This provides an explanation for tumor spread to contralateral mediastinal lymph nodes, and for routine investigation of the contralateral mediastinum by mediastinoscopy or PET. Of particular importance was the propensity for left lower lobe tumors to drain to the right paratracheal lymph node groups.

3. Mapping of lymph nodes to the appropriate station

The need for precise evaluation of lymph node status was identified in order to guide therapy, to estimate prognosis, to compare results from different institutions, and to conduct multi-institutional trials.

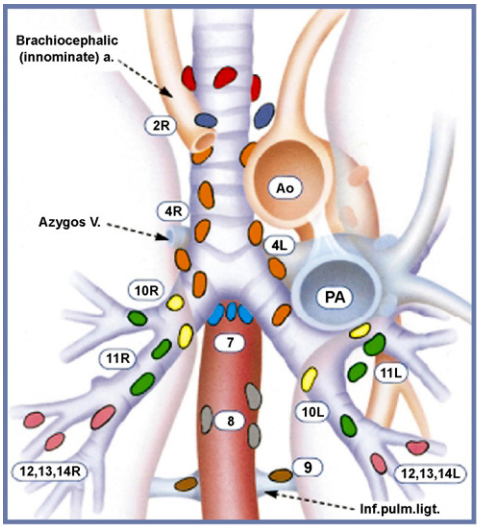

Fig. 1. Regional lymph node stations for lung cancer staging [2] (with kind permission from Chest to reproduce Fig. 1).

The evolution of lymph node mapping began with the 1978 report by Naruke et al. [8], when anatomical definitions were first used. In 1983, the American Thoracic Society produced a system in which the vague terms 'hilar' and 'mediastinal' were replaced with definitions of nodal levels based on constant anatomical landmarks which could be identified in the operating theatre [9]. In 1986, a Revised International Staging System was produced by the AJCC and UICC [1] in which the lymph node levels remained unchanged but the components of the N2 group changed and in which a N3 category was created. In 1997, the latest revised International Staging System was released [2] and a new pulmonary and mediastinal lymph node map proposed [10] (Fig. 1). In this latest revision the clinical staging system was based on CT landmarks making identification of stations 2 and 4 more difficult during surgery. Of importance was the inclusion of nodes along the anterior surface of the main stem bronchus within the pleural reflection line in station 4 (N2). Furthermore, the nodes in the midline should be classified as N2 rather than N3.

4. What are the persisting obstacles to lymph node mapping?

4.1. Anatomical allocation

The group identified five areas where difficulty exists in the interpretation of the definitions. These were: (1) the watershed between stations 2 and 4 in the paratracheal region; (2) the transition zone between station 4 and 10 at the tracheo-bronchial angle; (3) the border between station 7 in the subcarinal area and station nodes 10 on the medial side of the main stem bronchi; (4) the lower border of subcarinal station 7 and the beginning of paraesophageal station 8; and (5) the lymphatic watershed in the superior mediastinum which was proposed to be along the left margin of the trachea. Apart from the landmark of the take-off of the upper lobe bronchus from the main bronchus as a boundary between station 4 and 10, it was felt that the demarcation between these other stations was either arbitrary or not identifiable at mediastinoscopy or intraoperative staging. Most of these controversies are relevant because they either change clinical and pathological stage (according to the current TNM staging) in points 2, 3, and 5 above or may have prognostic implications as in 1 and 4.

The limitations of present nodal charts will be addressed in a new International Nodal Chart that will be included in the next revision of the UICC Staging System to be enacted in 2009.

4.2. Number of nodes (ratio) and number of stations

The importance of the number of investigated versus involved nodes and lymph node stations has not been addressed in the current staging systems. It is thought that the number of lymph node stations involved by tumor and their anatomical location are important prognostic factors [11].

5. Intraoperative lymph node assessment

5.1. General remarks

Although it is admitted that nodal staging of non-small cell lung cancer should be as accurate as possible, the extent of mediastinal lymph node assessment during surgery is controversial and there is no consensus.

Different techniques are used, ranging from simple visual inspection of the unopened mediastinum to an extended bilateral lymph node dissection. Furthermore, different terms are used to define these techniques.

There are data which clearly show that systematic sampling or nodal dissection improves intraoperative staging in contrast to selected lymph node sampling, especially in the detection of multi-level N2 disease [12,13].

The rate of occult N2 disease will also depend on the methods used for preoperative staging. Whether extending the lymph node dissection influences survival or recurrence rate of the disease remains to be determined [12–15].

A removal of at least six lymph nodes (UICC) from hilar and mediastinal stations is recommended to define nodal staging accurately and to determine pN0 status [16].

There is evidence that multi-level and multi-nodal disease or extracapsular involvement has a poorer prognosis [17].

5.2. Recommended definitions to describe intraoperative lymph node assessment

- Selected lymph node biopsy

  In this procedure, one or multiple suspicious lymph node(s) are biopsied. This is only justified to prove N1 or N2 disease in patients in whom resection is not possible (exploratory thoracotomy).
- Sampling

  Sampling is the removal of one or more lymph nodes guided by preoperative or intraoperative findings which are thought to be representative. Systematic sampling means a predetermined selection of the lymph node stations specified by the surgeon.
- Systematic nodal dissection

  All the mediastinal tissue containing the lymph nodes is dissected and removed systematically within anatomical landmarks. For left-sided tumors, in order to get access to the high and low paratracheal nodes, the division of the ligamentum arteriosus can be added, resulting in the mobilization of the aortic arch. It was recommended that at least three mediastinal nodal stations (but always subcarinal) should be excised as a minimum requirement. The nodes are separately labeled and examined histologically. Beside the mediastinal nodes, the hilar and the intrapulmonary lymph nodes are dissected as well [16].
- Lobe-specific systematic node dissection

  In this procedure, the mediastinal tissue containing specific lymph node stations are excised, depending on the lobar location of the primary tumor.
- Extended lymph node dissection

  In this procedure, bilateral mediastinal and cervical lymph node dissection is performed through median sternotomy and cervicotomy.

6. Recommendation

For complete resection of non-small cell lung cancer, a systematic nodal dissection is recommended in all cases [18,19]. Ideally, this should be done as an en-bloc resection, when possible of the upper mediastinal nodes on the right side (stations 2R and 4R), the limits of which are as follows: cranially, brachiocephalic trunk; medially, the ascending aorta and origin of aortic arch; anteriorly, the superior vena cava; posteriorly, the esophagus; and inferiorly, the pulmonary artery. Any visible nodes in front of the superior vena cava and/or posterior to the trachea should be removed (stations 3a and 3p). We can recommend the en-bloc resection of the lower mediastinum, including the fatty tissue from the diaphragm to the subcarinal space (stations 7, 8, and 9). On the left side, removal of the subaortic (station 5), para-aortic (station 6) and inferior paratracheal (4 L) lymph nodes is minimally required. For a complete nodal dissection of the left upper mediastinum, division of the ligamentum arteriosus allowing mobilization of the aortic arch is recommended, with special care not to injure the left recurrent laryngeal nerve.

It is important that the nodal stations are excised and put in different vials with separate labeling. The highest removed mediastinal node should be identified.

After pathological examination of the lymphadenectomy specimen, the number of involved lymph nodes and of the nodal stations, and the status of the nodal capsule should be documented.

Modifications in specific clinical situations

- For peripheral squamous T1, a more selective nodal dissection depending on the lobar location of the primary tumor (lobe-specific systematic nodal dissection) is acceptable, based on the detailed analysis of lobe-specific lymphatic drainage published by Naruke et al. [20] and Ichinose et al. [21]. It has been shown that the probability of unforeseen N2 disease is very low (<5%) in such patients [22,23].

  The Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery, based on Naruke's and Ichinose's findings, recommended a minimal dissection of at least three of the following mediastinal nodal stations depending on the lobar location of the primary tumor [24]. This implies dissection and histological examination of hilar and interlobar nodes which have to be tumor-free on frozen section analysis and the following lobe-specific node dissection is performed:

  right upper and middle lobe: 2R, 4R and 7;
  right lower lobe: 4R, 7, 8 and 9;
  left upper lobe: 5, 6 and 7;
  left lower lobe: 7, 8 and 9.

  In total, the lymphadenectomy specimen should include at least six nodes.
- After induction therapy, the same recommendation for lymph node assessment should be applied. However, lymph node dissection in the upper mediastinum after induction therapy (especially chemotherapy, radiotherapy after previous mediastinoscopy) may be technically difficult [25].
- High-risk patients.

  Intraoperative lymph node assessment can be minimized in high-risk patients undergoing minimal invasive video assisted wedge resections but if the patient can tolerate a lobectomy, standard recommendation of lymph node assessment should be followed [26].

7. Histopathological evaluation of the removed lymph nodes

7.1. Recommendations

Recommendations about the histopathological evaluation of the lymph nodes were published in 2001 by the 'Association of Directors of Anatomic and Surgical Pathology' [3]. However, in practice, there is no established consensus. The analysis of the nodes depends on the center, on the pathologist and it is often difficult to find a compromise between theoretical demands and practical feasibility. Some recommendations can be given to define quality criteria for this evaluation:

- As a first step, all resected intrapulmonary, hilar, and mediastinal nodes should be examined macroscopically. In the presence of gross tumor, one hematoxylin-eosin (HE) stained section should be performed at the most macroscopically suspicious site to demonstrate the metastasis and its possible extracapsular extension.
- If the macroscopic evaluation does not show any suspicion of metastasis, a single section of a node should be avoided. The probability to detect a metastasis on center section is related to the size of the lymph node, the size of the lesion, and the location of the tumor within the node [27]. To avoid this problem, it is recommended to perform several sections of the nodes, 2-mm slices in the longitudinal plane and to examine each block separately. Thin sections of 2 mm may increase the workload of the pathologist but increase the detection rate of metastases. Small nodes can be sliced and embedded in one block if possible.
- There are different methods to detect additional metastatic deposits in lymph nodes like serial sectioning or immunohistochemistry (IHC). IHC using a cocktail of cytokeratins such as the anti-epithelial antibody mAb Ber-Ep4, AE1/AE3 is a sensitive and specific method for detecting isolated tumor cells or clusters of cells. Three levels of section are enough for this analysis [28,29]. However, serial sectioning is relatively laborious and time-consuming and is therefore not practical as a routine [30].
- The report from the pathologist should describe the number of lymph nodes removed and studied, the overall number of metastatic lymph nodes in each station, and the status of the lymph node capsule.

7.2. Definition—micrometastasis

A micrometastasis can be detected by standard histopathology (HE staining), by IHC or by polymerase-chain reaction (PCR) (sensitive method).

A micrometastasis is defined as a lesion $\leq$2 mm in diameter compared with a metastasis which is larger than 2 mm [31]. It is obvious that the distinction between

micrometastasis and metastasis using the size as unique criterion is arbitrary.

Another important point is the distinction between micrometastasis and isolated tumor cells. Isolated tumor cells are defined as single tumor cells or small cell clusters, showing no stromal reaction and no proliferative potential. Isolated tumor cells can be detected by IHC, PCR or by other molecular methods, and their size $\leq$0.2 mm. Thus, histopathologically, the two terms 'micrometastasis' and 'isolated tumor cells' correspond to two different entities. However, in the literature, there is a mixture of different terminologies and the term micrometastasis is used for isolated cells, clusters of cells or true micrometastases according to the definition. Indeed, nearly all the published data are dealing with isolated cells and not with micrometastasis [32,33].

The incidence of isolated tumor cells is about 20—30%. This incidence was observed in several reports and also in patients with early-stage of NSCLC [34,35].

The detection of isolated tumor cells in the lymph nodes might have therapeutic implications, since several reports showed that isolated tumor cells are a significant negative prognostic factor in patients with NSCLC [36—38].

At the moment, the nodes with isolated tumor cells are not upstaged to N1 or N2 but are labeled pN0 (*i* positive or negative), or pN0 (mol positive or mol negative) if non-morphologic methods or PCR or other molecular methods have been used [39].

Isolated tumor cells may be observed at an early NSCLC stage and seem to predict a shortened recurrence-free interval and a shorter overall survival, indicating a biologically more aggressive tumor. As a consequence, it would be desirable to routinely analyze all HE negative nodes with IHC or other molecular methods. Whether the patients with isolated tumor cells would benefit from adjuvant therapies has to be evaluated in prospective trials.

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